Functional Human and Murine Tissue-Engineered Liver Is Generated From Adult Stem/Progenitor Cells.

Journal: Stem Cells Transl Med

Publication Year: 2016

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PubMed link: 27577096

Funding Grants: Gene therapy-corrected autologous hepatocyte-like cells from induced pluripotent stem cells for the treatment of pediatric single enzyme disorders

Public Summary:
Liver disease affects large numbers of patients, yet there are limited treatments available to replace absent or ineffective cellular function of this crucial organ. Donor scarcity and the necessity for immunosuppression limit one effective therapy, liver transplantation. But in some conditions such as inborn errors of metabolism, patients may be salvaged by providing partial amounts of liver tissue. After transplanting liver organoid units composed of a cells that includes adult stem and progenitor cells, both mouse and human tissue-engineered liver (TELi) form in animals. TELi contains normal liver components such as liver cells that express liver proteins that can be detected in the blood, and bile ducts and blood vessels. Sophisticated techniques to study mouse blood found breakdown products which supports the metabolic capability of human TELi being functional when transplanted into animals. Implanted TELi also grew in a mouse model of inducible liver failure, in this case, arginase deficiency. This approach could represent a personalized future therapy that would not require cellular reprogramming or immunosuppression to cure end-stage liver diseases.

Scientific Abstract:
: Liver disease affects large numbers of patients, yet there are limited treatments available to replace absent or ineffective cellular function of this crucial organ. Donor scarcity and the necessity for immunosuppression limit one effective therapy, orthotopic liver transplantation. But in some conditions such as inborn errors of metabolism or transient states of liver insufficiency, patients may be salvaged by providing partial quantities of functional liver tissue. After transplanting multicellular liver organoid units composed of a heterogeneous cellular population that includes adult stem and progenitor cells, both mouse and human tissue-engineered liver (TELi) form in vivo. TELi contains normal liver components such as hepatocytes with albumin expression, CK19-expressing bile ducts and vascular structures with alpha-smooth muscle actin expression, desmin-expressing stellate cells, and CD31-expressing endothelial cells. At 4 weeks, TELi contains proliferating albumin-expressing cells and identification of beta2-microglobulin-expressing cells demonstrates that the majority of human TELi is composed of transplanted human cells. Human albumin is detected in the host mouse serum, indicating in vivo secretory function. Liquid chromatography/mass spectrometric analysis of mouse serum after debrisoquine administration is followed by a significant increase in the level of the human metabolite, 4-OH-debrisoquine, which supports the metabolic and xenobiotic capability of human TELi in vivo. Implanted TELi grew in a mouse model of inducible liver failure. SIGNIFICANCE: The worldwide burden of liver disease is approximately 30 million cases. In 2010, there were more than 1 million global deaths from one cause of liver disease alone, cirrhosis. The only effective therapy for end-stage liver failure is liver transplantation, which is profoundly limited by scarce donor supply. In some conditions, such as inborn errors of metabolism or transient states of liver insufficiency, patients may be salvaged by providing partial quantities of functional liver tissue. In this study, it was hypothesized that a hardy multicellular cluster, or liver organoid unit, could be extracted from donor livers, which, after transplantation, would generate functional tissue-engineered liver. This novel cellular therapy would have several proposed advantages: an accessible in vivo hepatic replacement that can be monitored, more efficient stem/progenitor cell production (perfusion is not required and cellular loss is minimized), and durable function. This approach could represent a personalized future therapy that would not require cellular reprogramming or immunosuppression to cure end-stage liver diseases.